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Treatment-Related Upper Limb Morbidity 1 Year after Sentinel Lymph Node Biopsy or Axillary Lymph Node Dissection for Stage I or II Breast Cancer

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Background: In a prospective study, upper limb morbidity and perceived disability/activities of daily life (ADLs) were assessed before and 1 year after sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND).

Methods: A total of 204 patients with stage I/II breast cancer (mean age, 55.6 years; SD, 11.6 years) entered the study, and 189 patients (93%) could be evaluated after 1 year. Fifty-eight patients (31%) underwent only SLNB, and 131 (69%) underwent ALND. Assessments performed before surgery (t_0) and 1 year after surgery (t_1), included pain, shoulder range of motion, muscle strength, upper arm/forearm circumference, and perceived shoulder disability/ADL.

Results: Considerable treatment-related upper limb morbidity was observed. Significant ($P <$ .05) changes between t_0 and t_1 were found in all assessments except strength of elbow flexors. Patients in the ALND group showed significantly more changes in the range of motion in forward flexion, abduction, and abduction/external rotation; grip strength and strength of shoulder abductors; circumference of upper arm and forearm; and perceived shoulder disability in ADLs compared with the SLNB group. Multivariate linear regression analysis showed that ALND could predict a decrease of range of motion in forward flexion, abduction, strength of shoulder abductors, grip strength, and shoulder-related ADLs and an increase in the circumference of the upper arm. Radiation of the axilla (19 patients) predicts an additional decrease in shoulder range of motion.

Conclusions: One year after treatment of breast cancer, there is significantly less upper limb morbidity after SLNB compared with ALND. ALND is a predictor for upper limb morbidity.

Key Words: Breast cancer—Staging—Sentinel lymph node—Axillary dissection—Radiation—Morbidity.

The aim of modern breast cancer treatment is to obtain local tumor control, optimal lymph node staging with minimal treatment-related morbidity, good functional results, and, when possible, preservation of the breast. Axillary lymph node status is an important prognostic factor in patients with breast cancer.[1–4] Axillary lymph node dissection (ALND), however, is associated with upper limb morbidity such as pain, numbness, lymphedema, weakness, and impaired shoulder range of motion.[5–12] Upper limb morbidity can affect the ability to perform activities of daily life (ADLs) and quality of life.[11–18] Sentinel lymph node biopsy (SLNB) was introduced for staging of the axilla to reduce the number of unnecessary ALNDs.[19] SLNB is an accurate and safe procedure to predict metastatic disease in axillary lymph nodes and is widely accepted in breast cancer treatment.[19–23] SLNB is an excellent alternative for ALND in patients with clinically negative lymph nodes.[24] An increasing number of studies have evaluated SLNB-related

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morbidity in comparison with ALND-related morbidity.[22,23,25–35] Most of these studies have reported less morbidity for SLNB than for ALND.[23,25–36] A shortcoming in most studies is the absence of pretreatment assessment.

Fewer studies have investigated upper limb morbidity and perceived disability in ADLs after SLNB in comparison to ALND.[26,30,33] Generally, disability in ADLs of the SLNB group was less than for the ALND group.[26,30,33]

The aim of this study was to analyze prospectively the upper limb morbidity and perceived disability in ADLs of patients 1 year after SLNB versus ALND. Secondarily, it analyzed to which extent ALND and other treatment variables could predict upper limb morbidity and perceived disability.

PATIENTS AND METHODS

From June 1999 to June 2001, patients with breast carcinoma stage I or II participated in the study.[37] Patients were recruited from the University Hospital Groningen and the Martini Hospital Groningen. Informed consent was obtained from the participating patients. The protocol was approved by the institutional review boards of both hospitals. Two groups of breast cancer patients participated in the prospective study: patients who underwent conventional breast cancer treatment with ALND and patients who were treated according to the SLNB concept. Patients with positive sentinel lymph nodes subsequently received an ALND and were included in the ALND group.

Sentinel lymph nodes were identified by preoperative lymphoscintigraphy followed by intraoperative tracing with a gamma probe and Patent blue dye® (Blue Patenté, Labatoire Guerbet, Aulnay-sous-Bois, France). The procedure has been previously described in detail.[38] If pathologic examination revealed metastases in the sentinel lymph node, ALND was performed within 2 weeks after SLNB. Surgical and adjuvant treatments were used according to our protocol in both groups (Table 1).

Upper limb function and ADLs were assessed 1 day before surgery (t_0) and 1 year after surgery (t_1). Pain was assessed with a visual analog scale (VAS; Table 2). Patients were asked to mark their current pain on a 10-cm straight line (0 cm, no pain; 10 cm, worst pain imaginable).[39,40] Upper limb function was assessed by means of a physical examination according to a protocol (Table 2). Active shoulder range of motion was measured with a goniometer according to a standardized protocol in forward flexion, abduction, and external rotation.[40,41] Muscle strength of shoulder abductors and elbow flexors was measured with a handheld dynamometer (Citec®, Groningen, The Netherlands).[42–44] For assessment of grip strength, a Yamar® handheld dynamometer (Bollingbrook, Illinois, USA) was used.[45,46] All muscle strength measurements were performed three times, and the mean of these three measurements was used for further analysis. Upper arm and forearm circumferences were measured with a Gulick Measuring Tape® (Lafayette Instruments; model 258-J00305, Lafayette, Indiana, USA) at 10 cm proximal to the olecranon and 15 cm proximal to the styloid process of the ulnae.

ADLs were assessed with the Shoulder Disability Questionnaire (SDQ) and the Groningen Activity Restriction Scale (GARS). The SDQ is a functional status measure that covers 16 items. It was designed to evaluate

TABLE 1. *Tumor-node-metastasis classification, receptor status, and treatment characteristics of the included patients*

Variable	SLNB (n = 66)	ALND (n = 138)	Total (n = 204)
Patient age, y, mean (SD)	57.0 (11.9)	54.9 (11.3)	55.6 (11.6)
Tumor-node-metastasis classification			
Stage I	46 (70)	39 (28)	85 (42)
Stage IIA	15 (23)	71 (51)	86 (42)
Stage IIB	5 (8)	28 (20)	33 (16)
Estrogen-receptor status			
Positive	38 (58)	96 (70)	134 (66)
Negative	28 (42)	42 (30)	70 (34)
Surgical treatment of breast			
Mastectomy	17 (26)	68 (49)	85 (42)
Lumpectomy	49 (74)	70 (51)	119 (58)
Adjuvant therapies			
Radiotherapy of breast	49 (74)	70 (51)	119 (58)
Radiotherapy of axilla	0 (0)	19 (14)	19 (9)
Chemotherapy	10 (15)	59 (43)	69 (34)
Hormonal therapy	10 (15)	68 (49)	78 (38)

Data are n (%) unless otherwise noted.
SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

TABLE 2. *Assessment of shoulder function and activities of daily life (ADLs)*

Assessment	Assessment tool
Shoulder function	
Pain (current pain)	VAS[39,40] (cm)
Numbness	Clinical examination: numbness, yes or no
Active shoulder range of motion	Isomed® Inclinometer (Isomed, Portland, Oregon, USA)[40,41](°)
Forward flexion	
Abduction	
Combined abduction/external rotation	
External rotation	
Muscle strength	Citec® handheld dynamometer[42–44] (Nm)
Shoulder abductors	
Elbow flexors	
Grip strength (cylinder grip)	Yamar® handheld dynamometer[45,46] (Nm)
Circumference	
Upper arm circumference (10 cm proximal to the olecranon)	Gulick Measuring Tape (Lafayette Instrument; model 258-J00305) (cm)
Forearm circumference (15 cm proximal to the processus styloideus ulnae)	
ADLs	SDQ[47,48] GARS[49,50]

VAS, visual analog scale; SDQ, Shoulder Disability Questionnaire[47,48]; GARS, Groningen Activity Restriction Scale.[49,50]

the ability to perform daily activities in patients with shoulder disorders (shoulder-related ADLs).[47,48] It contains 16 statements that patients with shoulder disorders have used to describe in what kind of ADL situations they experience pain. It has a three-category response format: for example, 1, "Yes, my shoulder is painful when I open or close a door"; 2, "No, my shoulder is not painful when I open or close a door"; and 3, "I did not perform the activity during the past 24 hours." The total scoring range for the 16 statements was transformed to 0 to 100. A score of 0 means no functional status limitation, and a score of 100 means maximum functional status limitation (Table 2).[47,48]

The GARS assesses the perceived restrictions (disability) in performing 18 ADLs.[49,50] It has a four-category response format: 1, able to perform the activity without any difficulty; 2, able to perform the activity with some difficulty; 3, able to perform the activity with much difficulty; and 4, unable to perform the activity independently. The scoring range is 18 to 72. With a score of 18, the person can perform all the activities without any difficulty; with a score of 72, the person cannot perform any activity without the help of others (Table 2).[49,50]

Statistical analyses included descriptive statistics and *t*-tests for independent samples for between-group comparisons and *t*-tests for dependent samples for within-group comparisons. Pearson's χ^2 test was used for dichotomous variables. To discern to what extent treatment variables could predict upper limb morbidity and perceived disability, multivariate linear regression analyses were performed with the following independent variables: ALND, surgical treatment of the breast (modified radical mastectomy or lumpectomy), radiation of the axilla, and radiation of the breast. Differences were accepted as significant if P values were $<.05$.

RESULTS

From 1999 to 2001, 204 consecutive patients with invasive breast carcinoma were included in the study. Initially 124 patients (61%) underwent an SLNB; 58 patients (47%) subsequently underwent additional ALND because of metastasis in the sentinel node. Therefore, the study consisted of 66 patients (32%) with an SLNB and 138 patients (68%) with a level I or II ALND. Tumor-node-metastasis classification, receptor status, and treatment characteristics of the patients are listed in Table 1. At t_1, 189 patients could be evaluated: 58 patients (31%) in the SLNB group and 131 patients (69%) in the ALND group. Fifteen patients (7%) could not be assessed after 1 year. Seven patients were from the ALND group: two patients died of metastatic disease, two withdrew from the study because of distant metastases, and three withdrew because of psychological burden. Eight patients belonged to the SLNB group; one patient had distant metastasis, one refused further treatment, and six found the assessment protocol bothersome and chose to withdraw from the study although they had no upper limb complaints.

After 1 year, substantial treatment-related upper limb morbidity was observed for the entire study group (n = 189). Significant changes between t_0 and t_1 were found in all assessments except strength of the elbow flexors (Table 3). There was a small but significant increase in self-assessed pain perception (VAS) from .4 (SD, 1.1) to .8 (SD, 1.5). Numbness of the axillary region was observed in 119 patients (63%). The largest decrease in range of motion of the shoulder was found in abduction (15.7°; SD, 28.8°). Decreases in grip strength (16.8 Nm; SD, 48.0 Nm) and muscle strength of the shoulder abductors (11.4 Nm; SD, 31.9 Nm) were observed. At t_1, there was a minor but significant increase of upper arm circumference (.7 cm; SD, 1.7 cm) and forearm circumference (.4 cm; SD, 1.0 cm).

TABLE 3. *Upper limb morbidity and disability 12 months after breast cancer treatment (n = 189)*

Variable	Before surgery (mean ± SD)	12 mo after surgery (mean ± SD)	Change (mean ± SD)	*P* value
Pain (VAS: 0–10)	.4 ± 1.1	.8 ± 1.5	.4 ± 1.7	.001
Numbness (n)[a]	0	119	119	<.001
Forward flexion (°)	172.5 ± 11.8	166.3 ± 14.1	−6.2 ± 12.9	<.001
Abduction (°)	167.7 ± 22.7	152.0 ± 31.7	−15.7 ± 28.8	<.001
Abduction/external rotation (°)	87.0 ± 6.8	79.4 ± 14.4	−7.6 ± 13.4	<.001
External rotation (°)	67.7 ± 12.9	61.7 ± 12.7	−6.0 ± 12.6	<.001
Strength of shoulder abductors (Nm)	150.9 ± 36.8	139.5 ± 36.8	−11.4 ± 31.9	<.001
Strength of elbow flexors (Nm)	179.5 ± 41.2	179.5 ± 38.0	.0 ± 40.3	.999
Grip strength (Nm)	296.1 ± 65.1	279.3 ± 71.0	−16.8 ± 48.0	<.001
Circumference of upper arm (cm)	26.8 ± 3.0	27.5 ± 3.2	.7 ± 1.7	<.001
Circumference of forearm (cm)	24.3 ± 2.1	24.7 ± 2.2	.4 ± 1.0	<.001
SDQ (0–100)	7.9 ± 19.3	18.6 ± 27.9	10.7 ± 29.2	<.001
GARS (18–72)	19.7 ± 3.8	21.2 ± 5.2	1.5 ± 4.6	<.001

VAS, visual analog scale; SDQ, Shoulder Disability Questionnaire[47,48]; GARS, Groningen Activity Restriction Scale.[49,50]
[a]No standard deviations were given because it concerns a dichotomous variable.

Disability/ADLs increased as assessed with the SDQ (10.7; SD, 29.2) and the GARS (1.5; SD, 4.6; Table 3). Several changes in upper limb function (upper limb morbidity) and ADLs (perceived disability) between t_0 and t_1 were significantly different between the SLNB group and the ALND group, in favor of the first (Table 4).

No significant difference was found for the change in pain perception of both groups (Table 4). Numbness was observed in 10 patients (17%) of the SLNB group and in 109 patients (83%) of the ALND group at t_1 ($P < .001$; χ^2 test). For range of motion of the shoulder, the largest difference was found in shoulder abduction (14.5°; 95% confidence interval [CI], 22.0°–7.1°; Table 4). No difference was found in external rotation between groups. Significant differences were observed for grip strength (25.6 Nm; 95% CI, 40.8–10.3 Nm), strength of the shoulder abductors (14.9 Nm; 95% CI, 23.5–6.3 Nm), and, to a minor extent, strength of the elbow flexors (Table 4). The differences in circumference of the upper arm and forearm were significant (upper arm, .6 cm; 95% CI, .1–1.1 cm; forearm, .3 cm; 95% CI, .1–.6 cm; Table 4). Considering the increase in perceived disability in ADLs, a significant difference between the SLNB group and the ALND group was found for the SDQ (10.6; 95% CI, 2.5–18.7) but not for the GARS (1.0; 95% CI, −.1 to 2.1).

Multivariate linear regression analysis was performed to predict the mean change in upper limb function and

TABLE 4. *Change of upper limb function and disability in the SLNB group and the ALND group between t_1 (12 months after surgery) and t_0 (before surgery)*

Variable	SLNB (n = 58) ($t_1 - t_0$) (mean change ± SD)	ALND (n = 131) ($t_1 - t_0$) (mean change ± SD)	Differences in mean change, ALND − SLNB	
			Mean difference	*P* value
Pain (VAS: 0–10)	.2 ± 1.2	.6 ± 1.9	.4	.073
Numbness (n)[a]	10	109	99	<.001
Forward flexion (°)	−2.7 ± 10.0	−7.7 ± 13.7	5.0	.005
Abduction (°)	−5.6 ± 20.2	−20.1 ± 30.9	14.5	<.001
Abduction/external rotation (°)	−4.6 ± 7.9	−8.9 ± 15.0	4.3	.011
External rotation (°)	−4.6 ± 12.3	−6.6 ± 12.8	2.0	.324
Strength of shoulder abductors (Nm)	−1.0 ± 24.0	−15.9 ± 33.9	14.9	.001
Strength of elbow flexors (Nm)	7.5 ± 28.3	−3.3 ± 44.3	10.8	.048
Grip strength (Nm)	.0 ± 45.9	−25.6 ± 50.0	25.6	.001
Circumference of upper arm (cm)	.3 ± 1.2	.9 ± 1.8	.6	.019
Circumference of forearm (cm)	.2 ± .7	.5 ± 1.0	.3	.009
SDQ (0–100)	3.4 ± 23.5	14.0 ± 31.0	10.6	.011
GARS (18–72)	.8 ± 2.2	1.8 ± 5.4	1.0	.065

Results of *t*-test for independent samples.
SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; VAS, visual analog scale; SDQ, Shoulder Disability Questionnaire[46]; GARS, Groningen Activity Restriction Scale.[48]
[a]No standard deviations were given because it concerns a dichotomous variable.

ADLs between t_0 and t_1 for independent variables: axillary surgery (SLNB and ALND), surgery of the breast (breast-conserving surgery and mastectomy), radiation of the breast (no or yes), and radiation of the axilla (no or yes) (Table 5). ALND was a significant factor in the prediction of almost all mean changes in the performed assessments of upper limb function and ADLs (Table 5). Radiation of the axilla was also significant in four analyses (Table 5).

DISCUSSION

This study showed significant upper limb morbidity and associated ADL disabilities 1 year after treatment in breast cancer patients undergoing SLNB, ALND, or both. Patients undergoing SLNB had significantly less upper limb morbidity and fewer ADL disabilities 1 year after treatment compared with patients undergoing ALND.

This outcome confirms the assumption that SLNB is a less extensive surgical procedure that is associated with less upper limb morbidity compared with ALND. Several studies previously reported on morbidity after SLNB and ALND.[23,25–35] All studies reported less morbidity in patients after SLNB compared with ALND. However, there was considerable variability in study design. Only four studies used a preoperative assessment.[25,29,32,34] The follow-up period varied from 2 weeks to 3 years after surgical treatment.[32,33] Also, the assessment instruments varied from self-constructed questionnaires to physical examinations and some validated questionnaires. ADLs were assessed in only two studies.[26,30]

This study used a preoperative assessment. Additionally several reliable and validated measurement instruments were used to assess upper limb morbidity and perceived disability/ADLs.[40–42,44,46,48,49] In a recent systematic review, we emphasized the importance of the baseline assessment.[12] Preoperative assessment was also used by Leidenius et al.[32] and Peintinger et al.[34] The first study mentioned evaluated shoulder range of motion before surgery and 2 weeks and 3 months after surgery.[32] Differences in the prevalence of axillary web syndrome (20% of patients with SLNB and 72% patients of ALND) were held responsible for the differences in range of motion. Contrary to our findings, a normal range of motion was observed in almost all patients of both groups after 3 months. In that study, the author described only short-time morbidity.[32] Peintinger et al.[34] evaluated

TABLE 5. *Prediction of mean change in upper limb function and activities of daily life between t_0 and t_1 by means of linear regression analysis for independent variables: axillary surgery (SLNB = 0, ALND = 1), surgery of the breast (breast-conserving surgery = 0, mastectomy = 1), radiation of the breast (no = 0, yes = 1), and radiation of the axilla (no = 0, yes = 1)*

Dependent	Independent	β (95% CI)	r^2 Change
Forward flexion (°)	ALND	4.9 (.9–8.9)	.03
	Constant	2.7 (−.6 to 6.0)	
Abduction (°)	Radiation of axilla	19.5 (5.0–34.1)	.05
	ALND	11.6 (2.8–20.4)	.03
	Constant	5.6 (−1.5 to 12.7)	
Abduction/external rotation (°)	Radiation of axilla	7.4 (.7–14.2)	.03
	Constant	6.8 (4.8–8.7)	
External rotation (°)	Radiation of axilla	7.2 (.8–13.6)	.03
	Constant	5.1 (3.3–7.0)	
Strength of shoulder abductors (Nm)	ALND	14.1 (4.4–23.8)	.04
	Constant	1.0 (−7.1 to 9.1)	
Grip strength (Nm)	ALND	24.3 (9.3–39.3)	.05
	Constant	−.9 (−13.3 to 11.6)	
Circumference of upper arm (cm)	ALND	−.6 (−1.2 to .2)	.03
	Constant	−.3 (−.7 to .1)	
Circumference of forearm (cm)	Radiation of axilla	−.6 (−1.1 to .1)	.03
	Constant	−.4 (−.5 to .2)	
Shoulder Disability Questionnaire	ALND	−11.9 (−20.9 to 2.9)	.03
	Mastectomy	9.1 (.5–17.6)	.02
	Constant	−6.0 (−13.8 to 1.7)	

Only significant predictors are represented.

The larger the coefficient β, the larger the contribution of the independent variable to the explanation of the dependent variable. The r^2 change is a measure for the explained variance of the dependent variable by the independent variables. One hundred times r^2 change gives the percentage of explained variance. For instance, "Constant" is the mean change in the range of motion (ROM) for abduction when a patient received SLNB. When a patient received ALND, the mean ROM for abduction decreased another 11.6°, and when this patient also received radiation of the axilla, the mean ROM for abduction decreased another 19.5°.

$\Delta\text{Abd} = \text{C} + (.1)\text{ALND} \times 11.6 + (.1)\text{rad axilla} \times 19.5$

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CI, confidence interval.

pain, range of motion, and perceived disability (Karnofsky performance status scale [KPS]), in addition to quality of life, before to 1 year after ALND/SLNB. Similar to our results, they found significantly more pain (VAS), numbness, and change of abduction and flexion in the ALND group 1 year after treatment. In contrast to our results, patients perceived no disabilities (KPS) 1 year after treatment.[34] Maybe this was caused by their relatively small patient sample size ($n = 56$) or the different assessment instrument (KPS vs. SDQ/GARS). The KPS might be less sensitive for detecting small changes. Swenson et al.[30] assessed the side effects of ALND and SLNB with a self-constructed questionnaire (the Measure of Arm Symptom Survey) at 1, 6, and 12 months after surgery. At 12 months, they found significant differences in perceived pain, numbness, and limitations in range of motion in favor of the SLNB patients but found no difference between groups in interference with daily life.[30] The perceived disabilities in ADLs assessed in our study were relatively mild. Shoulder-related perceived disability assessed by the SDQ was significantly higher in the ALND group compared with the SLNB group. This significant difference was not found for the GARS. Probably the effect of axillary dissection is stronger for shoulder-related disabilities/ADLs than for disability in ADLs in general.

The SLNB group had a more favorable outcome than the ALND group with respect to adjuvant radiation on the axilla, chemotherapy, and hormonal therapy (Table 1). Relatively few ALND patients (19 of 138; 14%) received radiation on the axilla. Other studies reported effects of radiation on the axilla on shoulder range of motion.[12,18,45,51,52] The fact that patients who received radiation on the axilla naturally belonged to the ALND group may influence the comparison between SLNB and ALND concerning treatment-related morbidity.

Multivariate linear regression analysis to predict mean change in upper limb function and ADLs between t_0 and t_1 showed that ALND and radiation on the axilla were significant factors in the prediction of impaired range of motion (Table 5). Clinically, these findings indicate that concerning the decrease in range of motion in shoulder abduction, SLNB was responsible for 5.6° of the reduction, ALND was responsible for another 11.6°, and radiation on the axilla was responsible for another 19.5°. The effect of radiation on the axilla was most noteworthy for shoulder abduction, combined abduction/external rotation, and external rotation. These results suggest that radiation on the axilla affects the shoulder range of motion more than it affects muscle strength (Table 5). This confirms the results of some other studies[12,18,52] and may be explained by radiation-induced subcutaneous fibrosis affecting the range of motion.

ALND as a predictor of upper limb morbidity was observed for forward flexion, abduction, strength of shoulder abductors, grip strength, upper arm circumference, and shoulder-related ADLs (SDQ). These results confirm those of other studies in which the extent of axillary treatment was related to late morbidity.[12,15,33,52]

CONCLUSION

Significant treatment-related upper limb morbidity and associated ADL disabilities exist 1 year after SLNB or ALND. Treatment-related morbidity and shoulder-related perceived disability/ADLs (SDQ) are significantly lower 1 year after SLNB compared with ALND. ALND can predict upper limb morbidity and shoulder-related perceived disability/ADLs. Additional radiation on the axilla predicts a further decrease in shoulder range of motion.

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